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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
TAYLOR, J	
ART UNIT	PAPER NUMBER
1655	6

DATE MAILED: 10/03/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/721,550	REICH, NORBERT	
	Examiner	Art Unit	
	Janell Taylor Cleveland	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 22-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The following Office Action is NON-FINAL because new grounds of rejections are made.

Election/Restrictions

1. Newly submitted claim 21 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claim is drawn to a microarray substrate wherein the substrate is a bead, said bead having a surface area comprising attached probe molecules with a fluorescent label. This is considered a different invention than that of the claims already presented because it is not related to the first group.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 21 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites the phrase "c. contacting a substrate" however it is not clear if this substrate is the same as the original, first substrate, or is a second substrate. This could be clarified by amending the claim to read "second

substate" if that is applicable, or "the substrate" if it refers to the first substrate. Also, in step e., the step of removing the substrate from the sample is unclear for two reasons. First of all, it is not clear if this is the first or second substrate. Secondly, the word "remove" is unclear, because it is not clear if the entire sample is removed, including the hybridized portion, or if only the unhybridized portion is removed, or "washed" from the substrate. Also, the claim contains the phrase "level of label". This is unclear. This could be clarified by amending the claim to read "level of fluorescence emitted by the label". Appropriate correction is required.

4. Claim 27-30 recites the limitation "the second level". There is insufficient antecedent basis for this limitation in the claim. Appropriate correction is required.

5. Claim 30 also recites the phrase "complementary target level." It is not clear what is meant by this phrase. Claim 30 also recites the phrase "the second level approaches zero and the second level is greater than zero." Appropriate correction is required.

6. Claims 22-25 are drawn to methods, but no clear and defined steps are recited in the independent claims. It is unclear what the difference between the preamble and the process steps are. This could be corrected by inserting the word "comprising". Otherwise, it appears that all the steps are part of the preamble. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion. See Ex Parte Erlich, 3 USPQ2d, p. 1011 (Bd. Pat. App. Int. 1986.)

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) The invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

8. Claims 1, 2, 8, 9, and 22-31 are rejected under 35 U.S.C. 102(e) as being anticipated by McCasky et al (USPN 6,100,030).

Claim 1 is drawn to a substrate having a surface area, the surface area comprising attached labeled probe molecules. Claim 2 is drawn to the label being fluorescent. Claim 8 is drawn to the molecules being carbohydrates. Claim 9 is drawn to the substrate being a microarray. Claims 22-25 are drawn to a method for monitoring the hybridization of a probe and a target, providing a probe with a target. Claim 26 is drawn to a substrate having a plurality of probes, wherein said probes are fluorescently labeled, the labeled probe providing a detectable first level of fluorescence. Claim 27 is drawn to a substrate having a plurality of probes, wherein said probes are fluorescently labeled, the labeled probe providing a detectable first level of fluorescence, and when hybridized to a complementary target, wherein the second level is lower than the first level. Claim 28 is drawn to a substrate having a plurality of probes, wherein said probes are fluorescently labeled, the labeled probe providing a detectable first level of fluorescence, and when hybridized to a complementary target, wherein the second level is significantly lower than the first level. Claim 29 is drawn to a substrate having a

plurality of probes, wherein said probes are fluorescently labeled, the labeled probe providing a detectable first level of fluorescence, and when hybridized to a complementary target, wherein the second level approaches zero. Claim 30 is drawn to a substrate having a plurality of probes, wherein said probes are fluorescently labeled, the labeled probe providing a detectable first level of fluorescence, and when hybridized to a complementary target, wherein the second level approaches zero. Claim 31 is drawn to a substrate having a surface area, the surface area comprising attached labeled probe molecules, said probe further comprising a fluorescent label.

McCasky et al teaches an array which has a labeled probe attached. "Typically, a... probe is linked to a solid support and a target nucleic acid (e.g., a genomic nucleic acid, an amplicon, or, most commonly, an amplified mixture) is hybridized to the probe. Either the probe, or the target, or both can be labeled, typically with a fluorophore. Where the target is labeled, hybridization is detected by detecting bound fluorescence. Where the probe is labeled, hybridization is typically detected by quenching of the label. Where both the probe and the target are labeled, detection of hybridization is typically performed by monitoring a color shift resulting from proximity of the two bound labels..." (Col. 23, lines 38-45). Claim 8 is anticipated because nucleic acids comprise carbohydrates as part of their chemical structure. Also, claims 27-30 are anticipated because quenching results in a lower level of fluorescence, and may result in no fluorescence in some cases. Therefore, McCasky anticipates these claims.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky et al.

Claim 3 teaches that the fluorescent wavelength is between 300 and 700 nm.

McCasky et al teaches an array which has a labeled probe attached. "Typically, a... probe is linked to a solid support and a target nucleic acid (e.g., a genomic nucleic acid, an amplicon, or, most commonly, an amplified mixture) is hybridized to the probe. Either the probe, or the target, or both can be labeled, typically with a fluorophore. Where the target is labeled, hybridization is detected by detecting bound fluorescence. Where the probe is labeled, hybridization is typically detected by quenching of the label. Where both the probe and the target are labeled, detection of hybridization is typically performed by monitoring a color shift resulting from proximity of the two bound labels..." (Col. 23, lines 38-45).

McCasky does not teach the length of the fluoroescent wavelength.

It would have been obvious to one of ordinary skill in the art at the time of the invention that the wavelength would have been between 300-700nm, as it was well known in the art that the detectable range for fluorescent detection is between 200 and

800 nm. Therefore, this would have been within the acceptable range, and the range in which most fluorescent molecules are found.

11. Claims 4, 5, 10-13, 16-17, 19-20, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky in view of McGall et al.

Claim 4 is drawn to the labeled probe being comprised of native and nonnative nucleotides. Claim 5 is drawn to the nucleotides being nucleotide analogs. Claims 10-12 are drawn to the microarray being divided into quadrants wherein each different quadrant has labeled probe molecules of different sequences, and the amount of quadrants and probes on the microarray. Claim 13 is drawn to the microarray being a bead. Claims 16-17 and 19-20 is drawn to a method comprising detecting a difference in the probes before and after hybridization. Claim 32 is drawn to the method of claim 16, wherein multiple labeled probes and the multiplying of the labeled probes are achieved by a non-amplification step.

McCasky et al teaches an array which has a labeled probe attached. "Typically, a... probe is linked to a solid support and a target nucleic acid (e.g., a genomic nucleic acid, an amplicon, or, most commonly, an amplified mixture) is hybridized to the probe. Either the probe, or the target, or both can be labeled, typically with a fluorophore. Where the target is labeled, hybridization is detected by detecting bound fluorescence. Where the probe is labeled, hybridization is typically detected by quenching of the label. Where both the probe and the target are labeled, detection of hybridization is typically performed by monitoring a color shift resulting from proximity of the two bound labels..." (Col. 23, lines 38-45).

McCasky does not teach nucleotide analogs, or an array divided into quadrants, or a method wherein the levels of label are expressed twice and compared, or labeled probes achieved by non-amplification steps, or the amount of probe on the microarray.

As disclosed above, McGall et al. teaches "Oligonucleotide analogue arrays attached to solid substrates...target nucleic acids that comprise nucleotide analogs are bound to oligonucleotide analogue arrays." (Abstract). McGall also teaches that the "oligonucleotide probe arrays also comprise nucleotide analogues" (Col. 2, lines 50-51). McGall also teaches that the substrate may be a bead. (Col. 14 line 46). McGall also teaches detection by labeling probe molecules. (Col. 12 line 40).

It would have been obvious to combine McCasky and McGall because McGall teaches that "oligonucleotide analogues are resistant to hydrolysis or degradation by nuclease enzymes such as RNase A. This would have protected the probe from degradation.

McGall et al. does not specifically teach quadrants on the microarray, or the amount of probes on the microarray. McGall also does not teach measuring fluorescent levels before and after hybridization.

It would have been obvious to one of ordinary skill in the art to separate the areas of the microarrays into different quadrants having different probes. This was, in fact, well known in the art at the time of the invention. McGall et al. teaches "Provided that the spatial location of each probe in an array is known, the data from the probes is collected and processed to yield the sequence of a target irrespective of the physical arrangement of the probes on a chip." (Col. 15 lines 55-59). It would have therefore

been obvious to place the microarray into quadrants because the target was detectable as long as the area of the microarray was known. Furthermore, the amount of quadrants and probes on the array was well known and it would have been obvious that the range given would have worked with the array of McGall.

It would have been obvious to one of ordinary skill in the art to measure the level of fluorescence of a sample before and after hybridization. This would have been obvious because it was well known that this would have enabled one of ordinary skill to detect changes in the level of fluorescence due to hybridization.

It also would have been obvious to one of ordinary skill in the art at the time of the invention that labeled probe may be achieved by a non-amplification step. This would have been obvious because it was well known that probe may have arisen from genomic samples without the need of amplification.

12. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky and McGall et al as applied to claims above, and further in view of Gelfland et al. (USPN 5,804,375).

The claim is drawn to the nucleotide analog being 2-amino purine.

The teachings of McCasky and McGall et al. were discussed above.

McGall et al. does not teach 2-amino purine as the nucleotide analog.

Gelfland et al. teaches "...2-amino purine...is another analog that could be used in probe synthesis. The probes containing such nucleotide derivatives may be hydrolyzed to release much more strongly fluorescent mononucleotides..." (Col. 12, line 35).

It would have been obvious to one of ordinary skill in the art at the time of the invention that the nucleotide analog of McGall may have been 2-amino purine. This is because it was a well known nucleotide analog at the time of the invention, and was useful in that it produced a strong fluorescent signal when hydrolyzed. For this reason it would have been obvious to one of ordinary skill in the art to use it with the invention of McGall.

13. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky in view of McGall as applied to claims above, and further in view of Scholin et al. (USPN 6,187,530 B1).

Claim 7 is drawn to the probe molecule being comprised of amino acids.

The teachings of McCasky and McGall et al. are disclosed above.

McGall et al. does not teach an amino acid probe.

Scholin et al. teach antibody probes (Col. 9, line 59), which, of course, are comprised of amino acids, on an array.

It would have been obvious to one of ordinary skill in the art at the time of the invention that the probe of claim 1 may have been comprised of amino acids. This is because amino acid probes were well known in the art at the time of the invention and it was well known that they were capable of being used with an array, as in the one disclosed by Scholin et al.

14. Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky over McGall as applied to claims above, and further in view of Mandecki (USPN 6,001,571).

The claims are drawn to the bead being formed of ferromagnetic metal with a polymeric coating, and the amount of probes on the bead.

The teachings of McCasky and McGall et al. are disclosed above.

McGall does not teach that the bead is ferromagnetic, or the amount of probes contained thereon.

Mandecki teaches "In solid phase assays, small beads...are used to capture the analyte. Solid-phase microparticles may be made of different materials, such as glass...Some beads are made of ferromagnetic materials to facilitate their separation from complex suspensions of mixtures." (Col. 1 lines 20-26).

It would have been obvious to one of ordinary skill in the art at the time of the invention that the bead of McGall et al. may have been made up of ferromagnetic material, in order to facilitate its separation from complex suspension of mixtures. It would also have been obvious that a wide range in the number of probes attached to the beads may have been used, as this was well known in the art at the time of the invention.

15. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky in view of McGall as applied to claim 17 above, and further in view of Heagy et al. (USPN 5,753,516).

The claim is drawn to the method of claim 18, wherein the level of label expression is evaluated using a flow cytometer.

Neither McCasky nor McGall teaches the use of a flow cytometer (Col. 17, bridging col. 18).

Heagy et al. teaches the use of flow cytometry in detecting fluorescence.

It would have been obvious to combine these teachings as it was well known in the art that flow cytometry was capable of detecting fluorescence. It would have been obvious to use flow cytometry because it would have been useful in detecting the amount of fluorescence within a sample and gave specific numeric results which would have been comparable to one another.

Summary

16. Claim 21 is withdrawn from consideration. Claims 17, 22-25, and 27-30 are rejected under 35 U.S.C. 112, second paragraph. Claims 1, 2, 8, 9, and 22-31 are rejected under 35 U.S.C. 102(e) as being anticipated by McCasky et al. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky et al. Claims 4, 5, 10-13, 16-17, 19-20, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky in view of McGall et al. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky and McGall et al as applied to claims above, and further in view of Gelfland et al. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky in view of McGall as applied to claims above, and further in view of Scholin et al. Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky over McGall as applied to claims above, and further in view of Mandecki. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over McCasky in view of McGall as applied to claim 17 above, and further in view of Heagy. No claims are allowable.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janell Taylor Cleveland, whose telephone number is (703) 305-0273.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (703) 308-1152.

Any inquiries of a general nature relating to this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1634 via the PTO Fax Center using (703) 305-3014 or 305-4227. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989.)

Janell Taylor Cleveland

September 24, 2001

W. Gary Jones
Supervisory Patent Examiner
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9/28/01